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09/832,922	04/12/2001	Frederic Geissmann	1383-0260001	8471

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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 06/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/832,922	GEISSMANN ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,5,10 and 16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,5,10 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/8/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-2, 4-5, 10 and 16 are pending.

2. In view of the amendment filed 3/8/04, the following rejections remain.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-2, 4-5, 10 and 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a method of inhibiting retinol induced apoptosis of immature dendritic cells in vitro comprising contacting said dendritic cell with an effective amount of the specific retinol and an inflammatory cytokine wherein the retinol is selected from the group consisting of pan-RAR antagonist compound VIII (page 15 of the specification), RARα selective antagonist (Compound II), and RXR agonist SR11237 and compound V (4-[l-[5,6-Dihydro-3,5,5-trimethyl-8-(1-methylethyl)-2-naphthzenyl]-ethenyl] benzoic acid, (2) a method of enhancing antigen presentation of immature antigen presenting cell in vitro comprising contacting said dendritic cell with an effective amount of pan RXR agonist SR11237 and an inflammatory cytokine or RARα antagonist BMS749 and an inflammatory cytokine, **does not** reasonably provide enablement for (1) a method of "modulating" the immune system of any animal by affecting the physiology of any antigen-presenting cell in said mammal, comprising contacting said antigen-presenting cell with an effective amount of at least one of *any* "retinoid", and *any* cytokine such as TNF or IL1 active fragment thereof, any variant thereof, any analog thereof, and any derivative thereof under conditions whereby the "physiology" of said antigen presenting cell for treating *any* disease, (2) the method of "modulating" the immune system of any animal by affecting the physiology of any antigen-presenting cell in said mammal, comprising contacting said antigen-presenting cell with an effective amount of at least one of *any* "retinoid", and *any* cytokine under conditions whereby the "physiology" of said antigen presenting cell for treating *any* disease, wherein the effect upon said antigen presenting cell is activation of said cell, (3) the method of "modulating" the immune system of any animal by affecting the physiology of *any* antigen-presenting cell in said mammal, comprising contacting said antigen-presenting cell with

an effective amount of at least one of *any* "retinoid", and *any* cytokine under conditions whereby the "physiology" of said antigen presenting cell wherein the retinoid is any pan-RXR agonist, and any RAR antagonist such as any "Compound V", "Compound II", "compound VIII", any pharmaceutical acceptable salts, esters, and prodrugs thereof, (4) the said method wherein the cytokine is any TNFα variants, any TNFα analogues, any TNFα derivatives, any IL-1β "variants", any IL-1β "analogues" and any IL-1β derivatives thereof, and (5) the said method wherein the antigen is any dendritic cell, or any Langerhans cell for the claimed method of "modulating" the immune system of any animal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a method of inhibiting retinol induced apoptosis of immature dendritic cells in vitro comprising contacting said dendritic cell with an effective amount of the specific retinol and an inflammatory cytokine wherein the retinol is selected from the group consisting of pan-RAR antagonist compound VIII, RARα selective antagonist (Compound II), and RXR agonist SR11237 and compound V (4-[1-[5,6-Dihydro-3,5,5-trimethyl-8-(1-methylethyl)-2-naphthzenyl]-ethenyl] benzoic acid. The specification further discloses a method of enhancing antigen presentation of immature antigen presenting cell in vitro comprising contacting said dendritic cell with an effective amount of pan RXR agonist SR11237 and an inflammatory cytokine or a specific RARα antagonist BMS749 and an inflammatory cytokine. The specification also discloses that retinoic acid has been shown to either enhance or decrease immune responses depending on a number of factors such as the type of retinol used, the receptors, i.e., RARα, RARβ, RARγ, pan RAR, RXR, to which it binds, etc. However, the immunomodulating effect depends on the maturity of the dendritic cell as neither mature dendritic cell and monocytes died after exposure to retinoids (See paragraph bridging page 87 and

88). The specification on page 24 discloses that the antigen-presenting cells in the claimed methods may be any antigen-presenting cell, including but not limited to macrophages (including tissue-fixed macrophages, such as Kupffer cells, histiocytes, etc.), dendritic cells (including immature dendritic cells such as Langerhans cells), monocytes (and monocyte-derived antigen-presenting cells such as monocyte-derived macrophages), certain B cells, certain antigen-presenting epithelial cells, and the like. The specification on page 29 defines the term "cytokine" as growth factors, interleukins, colony-stimulating factors, interferon and lymphokines, which may be natural, synthetic, or Recombinant, analogues or homologues and TNFα analogues. The specification further defines "antigen-presenting cell" refers to any cell, regardless of the tissue derivation or source of the cell, that is involved in certain aspects of the immune response of an organism... Antigen-presenting cells are any cells capable of carrying out the process of antigen processing and presentation, including but not limited to macrophages (including tissue-fixed macrophages, such as Kupffer cells, histiocytes, etc.), dendritic cells (including immature dendritic cells such as Langerhans cells), monocytes (and monocyte-derived antigen-presenting cells such as monocyte-derived macrophages), certain B cells, certain antigen-presenting epithelial cells, and "the like".

The specification does not teach how to make *any* pan-RXR agonist, *any* RAR antagonist, any "Compound V", *any* "Compound II", *any* "Compound V", *any* "Compound VIII" and *any* ester and prodrug thereof, and *any* "analog", and *any* "derivatives" of TNFα or IL-1β for the claimed method for modulating immune system where the modulating of animal for the following reasons. First, The term "modulating" encompasses inhibitory as well as stimulatory activity, which are mutually exclusive. The specification does not teach which particular retinoid or retinoids in combination with which particular cytokine or cytokines would stimulate the immune system of the animal by affecting which physiology of APC in the animal for the claimed method. Likewise, the specification does not teach which particular retinoid or retinoids in combination with which particular cytokine or cytokines would inhibit the immune system of the animal by affecting which physiology of APC in the animal for the claimed method. Second, there is insufficient guidance as to the structure associated with function of all pan-RXR agonist, *all* RAR antagonist, analog, and *all* derivatives of TNFα and IL-1β because the term "agonist", "antagonist", "analog", "derivatives", "compound" and "active fragment" without the amino sequence have no structure. The said agonist, antagonist, analog, derivative, compound and active fragment could be a polynucleotide, a polypeptide, or a small organic molecule. Third,

there is insufficient guidance as to which modification within the retinoid would resulted in an agonist when binds to which receptor and which modification would result in an antagonist when binds to which particular retinoid receptor, much less combining with which cytokine that would resulted in either stimulating or inhibiting the immune system by affecting the physiology of APC. Fourth, there is insufficient guidance as how to make all TNF and IL1 active fragment, variant, analogues and derivative thereof for the claimed method.

Stryer *et al* teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

There is no recognition in the art that sequence with identity predicts biological function. Attwood *et al* teach that protein function is context-dependent and the state of the art of making functional assignments merely on the basis of some degree of similarity between sequences and the current structure prediction methods is unreliable.

Skolnick *et al.*, teach that squence-based methods for function prediction are inadequate and knowing a protein's structure does not necessary tell one it's function (See entire document, Abstract in particular).

Fifth, the immunomodulating effect depends on the maturity of the dendritic cell as neither mature dendritic cell and monocytes died after exposure to retinoids (See paragraph bridging page 87 and 88).

Sixth, not all retinol has been shown to enhance or decrease immune responses, depending on a number of factors such as the type of retinol used, the receptors, i.e., RARα, RARβ, RARγ, pan RAR, RXR, to which it binds, etc. Further, the term "modulating" can be stimulatory or inhibitory; the stimulatory and inhibitory actions are mutually exclusive.

Geissmann *et al* teach that retinol is metabolized intracellularly via two distinct pathways forming its active derivatives (a) retinoic acids (RAs), all-transRA (tRA), and 9-cis RA (9cRA) whose effects are transduced by retinoid receptors (RARs α, β or γ) and retinoic X receptors (RXRs). Geissmann *et al* further teach that only selective retinoids binding to certain receptors are capable can activate the specific type of antigen presenting cell or capable of

inducing apoptosis of certain type of antigen presenting cells such as immature dendritic cell (See entire document).

Given the indefinite number of undisclosed pan-RXR "agonist", RAR "antagonist", the diverse functions of each agonist, antagonist, analog and derivative of TNFα and IL-1β through distinct receptors pathways, it is unpredictable which one of said undisclosed pan-RXR "agonist", RAR "antagonist", TNFα and IL-1β "analog" and "derivatives" thereof would maintain the same structure and function, in turn, would be useful for modulating the immune system for treating any disease. Finally, Even if the claimed method is limited to the specific retinoids such as SR11237, there is no in vivo working example demonstrating that the claimed method is effective for modulating the immune system for treating any disease.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 3/8/04 have been fully considered but are not found persuasive.

Applicants' position is that page 38-58 of the specification disclose a large number of retinoids, including RAR agonist, RXR agonists and RAR antagonists. The specification discloses the sources where the structures and/or methods of synthesis of retinoid can be found. The specification goes on to discloses a number of ways in which cytokines, both natural and synthetic can be procured. The specification needs not disclose working example. One skill in the art cold use routine method of testing provided by the disclosure to determine the effects of various retinoids, cytokines and APCs in the method of the invention. The specification on page 58-72 disclose a number of methods to screen candidate compounds for their usefulness in the claimed invention.

However, the claims are not drawn to compound. The scope of claims in instant application encompasses a method of modulating the immune system of any animal by affecting

the physiology of antigen presenting cell (APC) in the animal by contacting the APC with a combination of any retinoid(s) and any cytokine(s). The term "modulating" encompasses inhibitory as well as stimulatory activity, which are mutually exclusive. The specification does not teach which particular retinoid or retinoids in combination with which particular cytokine or cytokines would stimulate the immune system of the animal by affecting which physiology of APC in the animal for the claimed method. Likewise, the specification does not teach which particular retinoid or retinoids in combination with which particular cytokine or cytokines would inhibit the immune system of the animal by affecting which physiology of APC in the animal for the claimed method. The specification discloses only a method of inhibiting retinol induced apoptosis of immature dendritic cells in vitro comprising contacting said dendritic cell with an effective amount of the specific retinol and an inflammatory cytokine wherein the retinol is selected from the group consisting of pan-RAR antagonist compound VIII, RARα selective antagonist (Compound II), and RXR agonist SR11237 and compound V (4-[l-[5,6-Dihydro-3,5,5-trimethyl-8-(1-methylethyl)-2-naphthzenyl]-ethenyl] benzoic acid. The specification further discloses a method of enhancing antigen presentation of immature antigen presenting cell in vitro comprising contacting said dendritic cell with an effective amount of pan RXR agonist SR11237 and an inflammatory cytokine or a specific RARα antagonist BMS749 and an inflammatory cytokine. The specification also discloses that retinoic acid has been shown to either enhance or decrease immune responses depending on a number of factors such as the type of retinol used, the receptors, i.e., RARα, RARβ, RARγ, pan RAR, RXR, to which it binds, etc. However, the immunomodulating effect depends on the maturity of the dendritic cell as neither mature dendritic cell and monocytes died after exposure to retinoids (See paragraph bridging page 87 and 88). The specification on page 24 discloses that the antigen-presenting cells in the claimed methods may be any antigen-presenting cell, including but not limited to macrophages (including tissue-fixed macrophages, such as Kupffer cells, histiocytes, etc.), dendritic cells (including immature dendritic cells such as Langerhans cells), monocytes (and monocyte-derived antigen-presenting cells such as monocyte-derived macrophages), certain B cells, certain antigen-presenting epithelial cells, and the like. The specification on page 29 defines the term "cytokine" as growth factors, interleukins, colony-stimulating factors, interferon and lymphokines, which may be natural, synthetic, or Recombinant, analogues or homologues and TNFα analogues. The specification further defines "antigen-presenting cell" refers to any cell, regardless of the tissue derivation or source of the cell, that is involved in certain aspects of the immune response of an

organism... Antigen-presenting cells are any cells capable of carrying out the process of antigen processing and presentation, including but not limited to macrophages (including tissue-fixed macrophages, such as Kupffer cells, histiocytes, etc.), dendritic cells (including immature dendritic cells such as Langerhans cells), monocytes (and monocyte-derived antigen-presenting cells such as monocyte-derived macrophages), certain B cells, certain antigen-presenting epithelial cells, and "the like".

The specification does not teach how to make *any* pan-RXR agonist, *any* RAR antagonist, any "Compound V", *any* "Compound II", *any* "Compound V", *any* "Compound VIII" and *any* ester and prodrug thereof, and *any* "analog", and *any* "derivatives" of TNFα or IL-1β for the claimed method for modulating immune system where the modulating of animal for the following reasons. First, The term "modulating" encompasses inhibitory as well as stimulatory activity, which are mutually exclusive. The specification does not teach which particular retinoid or retinoids in combination with which particular cytokine or cytokines would stimulate the immune system of the animal by affecting which physiology of APC in the animal for the claimed method. Likewise, the specification does not teach which particular retinoid or retinoids in combination with which particular cytokine or cytokines would inhibit the immune system of the animal by affecting which physiology of APC in the animal for the claimed method. Second, there is insufficient guidance as to the structure associated with function of all pan-RXR agonist, *all* RAR antagonist, analog, and *all* derivatives of TNFα and IL-1β because the term "agonist", "antagonist", "analog", "derivatives", "compound" and "active fragment" without the amino sequence have no structure. The said agonist, antagonist, analog, derivative, compound and active fragment could be a polynucleotide, a polypeptide, or a small organic molecule. Third, there is insufficient guidance as to which modification within the retinoid would resulted in an agonist when binds to which receptor and which modification would result in an antagonist when binds to which particular retinoid receptor, much less combining with which cytokine that would resulted in either stimulating or inhibiting the immune system by affecting the physiology of APC. Fourth, there is insufficient guidance as how to make all TNF and IL1 active fragment, variant, analogues and derivative thereof for the claimed method.

Stryer *et al* teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

There is no recognition in the art that sequence with identity predicts biological function. Attwood *et al* teach that protein function is context-dependent and the state of the art of making functional assignments merely on the basis of some degree of similarity between sequences and the current structure prediction methods is unreliable.

Skolnick *et al.*, teach that squence-based methods for function prediction are inadequate and knowing a protein's structure does not necessary tell one it's function (See entire document, Abstract in particular).

Fifth, the immunomodulating effect depends on the maturity of the dendritic cell as neither mature dendritic cell and monocytes died after exposure to retinoids (See paragraph bridging page 87 and 88).

Sixth, not all retinol has been shown to enhance or decrease immune responses, depending on a number of factors such as the type of retinol used, the receptors, i.e., RARα, RARβ, RARγ, pan RAR, RXR, to which it binds, etc. Further, the term "modulating" can be stimulatory or inhibitory; the stimulatory and inhibitory actions are mutually exclusive.

Geissmann *et al* teach that retinol is metabolized intracellularly via two distinct pathways forming its active derivatives (a) retinoic acids (RAs), all-transRA (tRA), and 9-cis RA (9cRA) whose effects are transduced by retinoid receptors (RARs α, β or γ) and retinoic X receptors (RXRs). Geissmann *et al* further teach that only selective retinoids binding to certain receptors are capable can activate the specific type of antigen presenting cell or capable of inducing apoptosis of certain type of antigen presenting cells such as immature dendritic cell (See entire document).

Given the indefinite number of undisclosed pan-RXR "agonist", RAR "antagonist", the diverse functions of each agonist, antagonist, analog and derivative of TNFα and IL-1β through distinct receptors pathways, it is unpredictable which one of said undisclosed pan-RXR "agonist", RAR "antagonist", TNFα and IL-1β "analog" and "derivatives" thereof would maintain the same structure and function, in turn, would be useful for modulating the immune system for treating any disease. Finally, even if the claimed method is limited to the specific retinoids such as SR11237, there is no in vivo working example demonstrating that the claimed method is effective

for modulating the "immune system" for treating any disease. Until the specific retinoid agonist or antagonist in combination with the specific cytokine or cytokines such as IL-1 or TNF analog, derivative or active fragment have been identified for the specific method of inhibiting the immune system or stimulating the immune system by affecting the physiology of the specific APCs, the specification as filed merely extends an invitation for one skill in the art for further experimentation to arrive at the claimed invention.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

5. Claims 1-2, 4-5, 10 and 16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) a method of "modulating" the immune system of any animal by affecting the physiology of any antigen-presenting cell in said mammal, comprising contacting said antigen-presenting cell with an effective amount of at least one of *any* "retinoid", and *any* cytokine under conditions whereby the "physiology" of said antigen presenting cell for treating *any* disease, (2) the method of "modulating" the immune system of any animal by affecting the physiology of any antigen-presenting cell in said mammal, comprising contacting said antigen-presenting cell with an effective amount of at least one of *any* "retinoid", and *any* cytokine under conditions whereby the "physiology" of said antigen presenting cell for treating *any* disease, wherein the effect upon said antigen presenting cell is activation of said cell, (3) the method of "modulating" the immune system of any animal by affecting the physiology of *any* antigen-presenting cell in said mammal, comprising contacting said antigen-presenting cell with an effective amount of at least one of *any* "retinoid", and *any* cytokine under conditions whereby the "physiology" of said antigen presenting cell wherein the retinoid is any pan-RXR agonist, and any RAR antagonist such as any "Compound V", "Compound II", "compound VIII", any pharmaceutical acceptable salts, esters, and prodrugs thereof, (4) the said method wherein the cytokine is any TNFα variants, any TNFα analogues, any TNFα derivatives, any IL-1β "variants", any IL-1β "analogues" and any IL-1β

derivatives thereof, and (5) the said method wherein the antigen is any dendritic cell, or any Langerhans cell for the claimed method of "modulating" the immune system of any animal.

The specification discloses only a method of inhibiting retinol induced apoptosis of immature dendritic cells in vitro comprising contacting said dendritic cell with an effective amount of the specific retinol and an inflammatory cytokine wherein the retinol is selected from the group consisting of pan-RAR antagonist compound VIII, RARα selective antagonist (Compound II), and RXR agonist SR11237 and compound V (4-[l-[5,6-Dihydro-3,5,5-trimethyl-8-(1-methylethyl)-2-naphthzenyl]-ethenyl] benzoic acid. The specification further discloses a method of enhancing antigen presentation of immature antigen presenting cell in vitro comprising contacting said dendritic cell with an effective amount of pan RXR agonist SR11237 and an inflammatory cytokine or a specific RARα antagonist BMS749 and an inflammatory cytokine. The specification also discloses that retinoic acid has been shown to either enhance or decrease immune responses depending on a number of factors such as the type of retinol used, the receptors, i.e., RARα, RARβ, RARγ, pan RAR, RXR, to which it binds, etc. However, the immunomodulating effect depends on the maturity of the dendritic cell as neither mature dendritic cell and monocytes died after exposure to retinoids (See paragraph bridging page 87 and 88). The specification on page 24 discloses that the antigen-presenting cells in the claimed methods may be any antigen-presenting cell, including but not limited to macrophages (including tissue-fixed macrophages, such as Kupffer cells, histiocytes, etc.), dendritic cells (including immature dendritic cells such as Langerhans cells), monocytes (and monocyte-derived antigen-presenting cells such as monocyte-derived macrophages), certain B cells, certain antigen-presenting epithelial cells, and the like. The specification on page 29 defines the term "cytokine" as growth factors, interleukins, colony-stimulating factors, interferon and lymphokines, which may be natural, synthetic, or Recombinant, analogues or homologues and TNFα analogues. The specification further defines "antigen-presenting cell" refers to any cell, regardless of the tissue derivation or source of the cell, that is involved in certain aspects of the immune response of an organism... Antigen-presenting cells are any cells capable of carrying out the process of antigen processing and presentation, including but not limited to macrophages (including tissue-fixed macrophages, such as Kupffer cells, histiocytes, etc.), dendritic cells (including immature dendritic cells such as Langerhans cells), monocytes (and monocyte-derived antigen-presenting cells such as monocyte-derived macrophages), certain B cells, certain antigen-presenting epithelial cells, and "the like".

Other than the specific combination of the specific retinoids and the specific inflammatory cytokines wherein the retinol is selected from the group consisting of pan-RAR antagonist compound VIII, RARα selective antagonist (Compound II), and RXR agonist SR11237 and compound V (4-[l-[5,6-Dihydro-3,5,5-trimethyl-8-(1-methylethyl)-2-naphthzenyl]-ethenyl] benzoic acid for inhibiting the retinol induced apoptosis of immature dendritic cells and the specific combination of pan RXR agonist SR11237 and an inflammatory cytokine or the specific RARα antagonist BMS749 and an inflammatory cytokine for a method of stimulating antigen presentation of immature antigen presenting cell, the other combinations of undisclosed retinoid and cytokine for the claimed method of inhibiting or stimulating the immune system of an animal are not adequately described. Further, there is insufficient written description about the structure associated with function of *all* "Pan-RXR agonist", *all* "RAR antagonist", *all* "variants", all "derivatives", "analogues" and "active fragment" of TNFα or IL-1β because the term "agonist", "antagonist", "analog", "derivatives", "compound" and "active fragment" without the amino acid sequence or nucleotide sequence have no structure, much less function. Even if the method is limited to the specific retinoids and the specific cytokine, the method of modulating the immune system of an animal by affecting the "physiology" of *any* antigen-presenting cell such as mature APC, macrophage, monocytes, Kupffer cells, and histiocytes, is not adequately described because the specification discloses that the immunomodulating effect of the specific retinoid and TNF alpha is limited to immature dendritic cells. Further, the specification discloses only a method for the inducing apoptosis and antigen presentation of immature dendritic cells *in vitro*, the claimed method of modulating the immune system of an animal wherein modulating can be inhibitory or stimulating by affecting any physiology of any antigen-presenting cell in said animal is not adequately described. Given the lack of additional representative species of antigen presenting cell, and the combination of various retinoids and various cytokines for the claimed method, one of skill in the art would conclude that Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Final Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 3/8/04 have been fully considered but are not found persuasive.

Applicants' position is that the specification provides sufficient written description to convey to one of ordinary skill that applicants had possession of the full scope of the claimed invention upon filing of the application.

The scope of claims in instant application encompasses a method of modulating the immune system of any animal by affecting the physiology of antigen presenting cell (APC) in the animal by contacting the APC with a combination of any retinoid(s) and any cytokine(s). The term "modulating" encompasses inhibitory as well as stimulatory activity, which are mutually exclusive. The specification does not describe which particular retinoid or retinoids in combination with which particular cytokine or cytokines would stimulate the immune system of the animal by affecting which physiology of APC in the animal for the claimed method. Likewise, the specification does not describe which particular retinoid or retinoids in combination with which particular cytokine or cytokines would inhibit the immune system of the animal by affecting which physiology of APC in the animal for the claimed method. The specification discloses only a method of inhibiting retinol induced apoptosis of immature dendritic cells in vitro comprising contacting said dendritic cell with an effective amount of the specific retinol and an inflammatory cytokine wherein the retinol is selected from the group consisting of pan-RAR antagonist compound VIII, RARα selective antagonist (Compound II), and RXR agonist SR11237 and compound V (4-[l-[5,6-Dihydro-3,5,5-trimethyl-8-(1-methylethyl)-2-naphthzenyl]-ethenyl] benzoic acid. The specification further discloses a method of enhancing antigen presentation of immature antigen presenting cell in vitro comprising contacting said dendritic cell with an effective amount of pan RXR agonist SR11237 and an inflammatory cytokine or a specific RARα antagonist BMS749 and an inflammatory cytokine. The specification also discloses that retinoic acid has been shown to either enhance or decrease immune responses depending on a number of factors such as the type of retinol used, the receptors, i.e., RARα, RARβ, RARγ, pan RAR, RXR, to which it binds, etc.

Other than the specific combination of the specific retinoids and the specific inflammatory cytokines wherein the retinol is selected from the group consisting of pan-RAR antagonist compound VIII, RARα selective antagonist (Compound II), and RXR agonist SR11237 and compound V (4-[l-[5,6-Dihydro-3,5,5-trimethyl-8-(1-methylethyl)-2-naphthzenyl]-ethenyl] benzoic acid for inhibiting the retinol induced apoptosis of immature dendritic cells and the specific combination of pan RXR agonist SR11237 and an inflammatory cytokine or the specific RARα antagonist BMS749 and an inflammatory cytokine for a method of stimulating

antigen presentation of immature antigen presenting cell, the other combinations of undisclosed retinoid and cytokine for the claimed method of inhibiting or stimulating the immune system of an animal are not adequately described. Further, there is insufficient written description about the structure associated with function of *all* "Pan-RXR agonist", *all* "RAR antagonist", *all* "variants", all "derivatives", "analogues" and "active fragment" of TNFα or IL-1β because the term "agonist", "antagonist", "analog", "derivatives", "compound" and "active fragment" without the amino acid sequence or nucleotide sequence have no structure, much less function. Even if the method is limited to the specific retinoids and the specific cytokine, the method of modulating the immune system of an animal by affecting the "physiology" of *any* antigen-presenting cell such as mature APC, macrophage, monocytes, Kupffer cells, and histiocytes, is not adequately described because the specification discloses that the immunomodulating effect of the specific retinoid and TNF alpha is limited to immature dendritic cells. Further, the specification discloses only a method for the inducing apoptosis and antigen presentation of immature dendritic cells *in vitro*, the claimed method of modulating the immune system of an animal wherein modulating can be inhibitory or stimulating by affecting any physiology of any antigen-presenting cell in said animal is not adequately described. Given the lack of additional representative species of antigen presenting cell, and the combination of various retinoids and various cytokines for the claimed method, one of skill in the art would conclude that Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Final Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Trinchieri *et al* (Blood 69(4): 1218-24, April 1987; PTO 892).

Trinchieri *et al* teach a method of modulating the immune system of an animal by affecting the physiology such as differentiation of undifferentiated promyelocytic HL60 (non-

adherence) to differentiated (adherent) monocyte and/macrophage phenotype (antigen presenting cells) with a retinoid such as retinoic acid and a cytokine such as tumor necrosis factor (TNFα) (See abstract, in particular). The reference monocyte and/macrophage cell is an antigen presenting cell as defined on page 29 of instant specification. Trinchieri *et al* teach that the combination of tumor necrosis factor (TNFα) and retinoic acid is useful for inducing differentiation and growth inhibition of human promyelocytic leukemia (See Discussion, in particular). Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed 3/8/04 have been fully considered but are not found persuasive.

Applicants' position is that Trichieri et al do not disclose acquisition of antigen presenting capability by differentiated HL-60 cells. Because the limitation of antigen presenting cell limitation is not met in claim 1, it is also necessarily not met in claim 10.

However, the specification on page 29 defines antigen presenting cells as "*any cell*, regardless of the tissue derivation or source of the cell, ...Antigen-presenting cells are any cells capable of carrying out the process of antigen processing and presentation, including but *not limited to* macrophages (including tissue-fixed macrophages, such as Kupffer cells, histiocytes, etc.), dendritic cells (including immature dendritic cells such as Langerhans cells), monocytes (and monocyte-derived antigen-presenting cells such as monocyte-derived macrophages), certain B cells, certain antigen-presenting epithelial cells, and *the like*". The reference HL60 cell line are monocytic origin. Trinchieri *et al* teach a method of modulating the immune system of an animal by affecting the physiology such as differentiation of undifferentiated promyelocytic HL60 (non-adherence) to differentiated (adherent) monocyte and/macrophage phenotype (antigen presenting cells) with a retinoid such as retinoic acid and a cytokine such as tumor necrosis factor (TNFα) (See abstract, in particular).

In response to applicant's argument that the reference fails to show certain features of applicant's invention, it is noted that the features upon which applicant relies (acquisition of antigen presenting capabilities" are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1-2, 10 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dunlop *et al* (Exp Dermatol 3(5):204-11, Oct 1994; PTO 892) in view of Zhou *et al* (Proc. Natl. Acad. Sci USA 93: 2588-2592, March 1996; PTO 892) or Hausser *et al* (Immunobiology. 197(5):534-42, Nov 1997; PTO 892) or Cumberbatch *et al* (Arch Dermatol Res. 289(5):277-84, Apr 1997; PTO 892).

Dunlop *et al* teach a method of modulating the immune system of an animal such as mice by affecting the physiology such as cell maturation and allogeneic cell-stimulating capability of antigen-presenting cell such as Langerhans cell from the skin by administering a retinoid such as all-trans retinoic acid (See abstract, in particular).

The claimed invention in claim 1 differs from the teachings of the reference only that the method comprises contacting said antigen-presenting cell with an effective amount of at least one retinoid and an effective amount of at least one cytokine whereby the physiology of said antigen-presenting cell is affected.

The claimed invention in claim 10 differs from the teachings of the reference only that the method wherein the cytokine is TNFα or IL-1 beta.

Zhou *et al* teach that dendritic cells such as monocytes derived dendritic cell or Langerhans cell in the epidermis of the skin are the most potent antigen-presenting cells (See page 2588, column 1, in particular). Zhou *et al* further teach that cytokine treatment such as GM-

CSF, IL4 or TNFα induces monocyte derived dendritic cell differentiation by acquiring CD83+, dendritic cell morphology, and the capacity of said cell to present antigen to T cell that can be measured by mixed leukocyte reactions (See Figure 4B, page 2591, column 1, in particular).

Hausser *et al* teach that treating monocyte derived dendritic cell (mdDC) with TNF or soluble CD40L led to enhanced MHC and accessory surface antigen expression with significantly elevated T cell stimulatory activity (See abstract, in particular).

Cumberbatch *et al* teach that intradermal administration of TNF-alpha or IL-1 activate Epidermal Langerhans cells (LC), characterized by the acquisition of a more dendritic morphology and the increased expression of Ia molecules. Cumberbatch *et al* further teach that both IL-1 beta and TNF-alpha can each stimulate the migration of epidermal LC, but that the changes induced by these cytokines are not identical (See abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modulate the immune system as taught by Dunlop *et al* by including cytokine such as TNF alpha that activates antigen presenting cell as taught by Zhou *et al,* Hausser *et al* or Cumberbatch *et al* or cytokine such as IL-1 beta as taught by Cumberbatch *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Zhou *et al* further teach that cytokine treatment such as GM-CSF, IL4 or TNFα induces monocyte derived dendritic cell differentiation by acquiring CD83+, dendritic cell morphology, and the capacity of said cell to present antigen to T cell that can be measured by mixed leukocyte reactions (See Figure 4B, page 2591, column 1, in particular). Hausser *et al* teach that treating monocyte derived dendritic cell (mdDC) with TNF or soluble CD40L led to enhanced MHC and accessory surface antigen expression with significantly elevated T cell stimulatory activity (See abstract, in particular). Cumberbatch *et al* teach that intradermal administration of TNF-alpha or IL-1 activate Epidermal Langerhans cells (LC), characterized by the acquisition of a more dendritic morphology and the increased expression of Ia molecules.

Applicants' arguments filed 3/8/04 have been fully considered but are not found persuasive.

Applicants' position is that Dunlop et al, and Zhou et al or Hassuer et al or Cumberbatch et al provide no suggestion or motivation to one of ordinary skill to combine their disclosures, nor is there knowledge generally available to those of ordinary skill in the art that provides such

motivation or suggestion. There is also no suggestion of a reasonable likelihood of success in making or using the claimed invention as a result of combining the cited references. The Examiner has taken selected portions of isolated disclosures and reconstructed them in an attempt to render the claimed invention obvious. This is impermissible hindsight reconstruction that fails to establish a prima facie case of obviousness.

In response to applicants' arguments that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine 5 USPQ2d 1596 (Fed. Cir 1988) and In re Jones 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the teachings of Duplop pertaining to the method of modulating the immune system of an animal such as mice by affecting the physiology such as cell maturation and allogeneic cell-stimulating capability of antigen-presenting cell such as Langerhans cell from the skin by administering a retinoid such as all-trans retinoic acid and the teachings of Zhou *et al* indicating success in inducing antigen presenting cell such as monocyte derived dendritic cell differentiation by administering cytokines such as GM-CSF, IL4 or TNFα (See Figure 4B, page 2591, column 1, in particular) or the teachings of Hausser *et al* indicating success in inducing antigen presenting cell such as monocyte derived dendritic cell (mdDC) activation by administering cytokines such as TNF (See abstract, in particular) or the teachings of Cumberbatch *et al* indicating success in inducing antigen presenting cell such as Epidermal Langerhans cells (LC) differentiation as measured by acquisition of a more dendritic morphology by treating with TNF-alpha and IL-1 (See abstract, in particular). The success in inducing APC differentiation and activation taught by the cited references would have led one of ordinary skill in the art at the time the invention was made to combine the references to modulate the immune system by affecting the physiology of antigen-presenting cells. The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983) see MPEP 2144.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on

obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. In re McLaughlin , 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). See MPEP 2145.

11. Claims 4-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dunlop *et al* (Exp Dermatol 3(5): 204-11, Oct 1994; PTO 892) in view of Zhou *et al* (Proc. Natl. Acad. Sci USA 93: 2588-2592, March 1996; PTO 892) or Hausser *et al* (Immunobiology. 197(5): 534-42, Nov 1997; PTO 892) or Cumberbatch *et al* (Arch Dermatol Res. 289(5): 277-84, Apr 1997; PTO 892) as applied to claims 1-2, 10 and 16 mentioned above and further in view of US Pat 5,552,271 (Sept 1996, PTO 1449).

The combined teachings of Dunlop *et al*, Zhou *et al*, Hausser *et al* and Cumberbatch *et al* have been discussed supra.

The claimed invention in claim 4 differs from the combined teachings of the references only in that the method wherein the retinoid is a pan-RSR agonist and an RAR antagonist.

The claimed invention in claim 5 differs from the combined teachings of the references only that the method wherein the pan-RXR agonist is SR11237 and pharmaceutically acceptable salts, esters and prodrugs thereof.

The '271 patent teaches a method of inhibiting an activity of a retinoid X receptor heterodimer formation using a pan-RXR agonist such as SR11237 (See entire document, abstract, column 12, line 20-35, in particular). The '271 patent further teaches retinoids are important therapeutics I the treatment of skin diseases and cancers (See col. 1, lines 14-16, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the retinoid in the method of modulating immune system of an animal as taught by Dunlop *et al* for the various retinoid such as pan-RXR agonist is SR11237 as taught by the '271 patent in combination with various cytokine such as TNFα as taught by Zhou *et al,* Hausser *et al*, or Cumberbatch *et al* or IL1β as taught by Cumberbatch *et al* for modulate the immune system by affecting one of the physiology of antigen presenting cells as taught by Dunlop *et al,* Zhou *et al,* Hausser *et al*, and Cumberbatch *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '271 patent teaches that pan-RXR agonist such as SR11237 is useful as a method of inhibiting an activity of a retinoid X receptor heterodimer formation (See entire document, abstract, column 12, line 20-35, in particular) and retinoids are important therapeutics I the treatment of skin diseases and cancers (See col. 1, lines 14-16, in particular). Zhou *et al* further teach that cytokine treatment such as GM-CSF, IL4 or TNFα induces monocyte derived dendritic cell differentiation by acquiring CD83+, dendritic cell morphology, and the capacity of said cell to present antigen to T cell that can be measured by mixed leukocyte reactions (See Figure 4B, page 2591, column 1, in particular). Hausser *et al* teach that treating monocyte derived dendritic cell (mdDC) with TNF or soluble CD40L led to enhanced MHC and accessory surface antigen expression with significantly elevated T cell stimulatory activity (See abstract, in particular). Cumberbatch *et al* teach that intradermal administration of TNF-alpha or caused the activation of Epidermal Langerhans cells (LC), characterized by the acquisition of a more dendritic morphology and the increased expression of Ia molecules. Cumberbatch further teach that both IL-1 beta and TNF-alpha can each stimulate the migration of epidermal LC to site of infection (See abstract, Discussion, in particular).

Applicants' arguments filed 3/8/04 have been fully considered but are not found persuasive.

Applicants' position is that there is no suggestion or motivation in the cited references that would led one of ordinary skill to combine Dunlop et al, and Zhou et al or Hassuer et al or Cumberbatch et al or the '271 patent and that would also suggest a reasonable likelihood of success in making or using the claimed invention as a result of combining the cited references. The Examiner has taken selected portions of isolated disclosures and reconstructed them in an attempt to render the claimed invention obvious. This is impermissible hindsight reconstruction that fails to establish a prima facie case of obviousness.

In response to applicants' arguments that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine 5 USPQ2d 1596 (Fed. Cir 1988) and In re Jones 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the teachings of Duplop pertaining to the method of modulating the immune system of an animal such as mice by

affecting the physiology such as cell maturation and allogeneic cell-stimulating capability of antigen-presenting cell such as Langerhans cell from the skin by administering a retinoid such as all-trans retinoic acid and the teachings of the '271 patent pertaining to the importance of retinoids and pan-RXR agonist such as SR11237 (See entire document, abstract, column 12, line 20-35, in particular) in therapeutics treatment of skin diseases and cancers (See col. 1, lines 14-16, in particular). Zhou *et al* indicating success in inducing antigen presenting cell such as monocyte derived dendritic cell differentiation by administering cytokines such as GM-CSF, IL4 or TNFα (See Figure 4B, page 2591, column 1, in particular) or the teachings of Hausser *et al* indicating success in inducing antigen presenting cell such as monocyte derived dendritic cell (mdDC) activation by administering cytokines such as TNF (See abstract, in particular) and the teachings of Cumberbatch *et al* indicating success in inducing antigen presenting cell such as Epidermal Langerhans cells (LC) differentiation as measured by acquisition of a more dendritic morphology by treating with TNF-alpha and IL-1 (See abstract, in particular) would have led one of ordinary skill in the art at the time the invention was made to combine the references to solve a well known problem in the art. The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983) see MPEP 2144.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. In re McLaughlin , 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). See MPEP 2145.

12. No claim is allowed.

13. **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (703) 872-9306.

15. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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